Formulation and Evaluation of Sprue Gel Preparations of Betel Leaf Extract (*Piperis betle L.*)

Minda Warnis(✉), Ilham Marsandes, Atun Rohayati, Besse Mawaddah, and Dewi Marlina

Politeknik Kesehatan Kemenkes Palembang, Palembang, Indonesia
mindarwis@poltekkespalembang.ac.id

Abstract. Sprue is a disease that is often found in daily activities due to infection with the fungus Candida albicans. The community uses betel leaves to treat sprue by chewing the betel leaf until it is crushed, leaving it in the mouth for a while, especially on the affected area. The chemical content of betel leaf extract is saponins, flavonoids, and essential oil s that can treat sprue. The betel leaf extract was formulated into a gel preparation with variations of carbopol 934 and xanthan gum as a gelling agent. The purpose of this study was to formulate a stable and eligible betel leaf extract gel. This research is an experimental study by making several gel formulas using variations of carbopol 934 and xanthan gum at a concentration ratio of 1%:1%, 1.25%:0.75%, 0.75%:1.25% and addition of 10% betel leaf extract. Then performed an evaluation of the preparation for 28 days of storage, including pH, viscosity, homogeneity, dispersibility, syneresis/swelling, color, odor, and irritation. The results showed that the pH, viscosity, syneresis/swelling, dispersibility, homogeneity, color, odor, and irritation met the requirements for all three formulas for 28 days of storage. Betel leaf extract (Piperis betle L.) can be formulated into a gel preparation that is stable and meets the requirements. The best formula is produced with variations of carbopol 934 and xanthan gum 1%:1%.

Keywords: Betel leaf · Sprue gel · Gelling agent · Carbopol · Xanthan gum

1 Introduction

Thrush is an ulcerated lesion that occurs recurrence in the oral mucosa [1]. Thrush is caused by an infection that is most often caused by the fungus Candida albicans [2]. This mushroom is one of the mushrooms which are pathogenic if the amount is excessive.

In early 2018 there was a case of withdrawal of thrush products by the Food and Drug Administration (BPOM). According to [3], in terms of oral disease, all canker sores are not allowed to use policresulen, and there are also no scientific studies that prove the content of these products can cure diseases or disorders of the oral cavity, such as canker sores. According to [4], the use of policresulen in the form of a 36% concentrated external dr ug liquid dosage form has not been approved, due to the absence of supporting scientific evidence and studies, and in the long term the use of policresulen can cause

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chemical burns to the oral mucosa of consumers. So many people use traditional medicine to cure canker sores. One of them is betel leaf (Piperis betle L.) which is believed to cure canker sores.

Betel leaf contains flavonoids, saponins, tannins, terpenoids, phenols, and essential oils [5]. Essential oil of betel leaf has MIC against Candida albicans at a concentration of 10% [6]. Utilization of betel plants by the community by chewing betel leaves until crushed. Leave it in the mouth for a while, especially in the area affected by canker sores [7]. The traditional way of using it is less efficient and effective, so that efforts are needed to optimize the efficacy, cover the unpleasant taste, as well as create a formula that provides comfort and ease of use, namely by making gel preparations.

Betel leaf extract gel is a gel preparation for use on the oral mucosa with a hydrophilic gel base material and the main raw material is betel leaf extract. Examples of hydrophilic gel bases include polyacrylic acid (carbopol), Sodium Carboxy Methyl Cellulose (Na CMC), non-ionic cellulose esters, and polysaccharides (xanthan gum).

According to [8], xanthan gum and carbopol 934 are considered non-toxic and non-irritating if used in a predetermined concentration range, and have been shown to have no adverse effects in animal tests. In addition, variations of xanthan gum and carbopol 934 as gelling agents were chosen because the combination of the two types of gelling agents gave a mucoadhesive effect, because these gels functioned by being affixed to the wound mucosa, so the combination of the two aims to prolong the contact time of the preparation with the target location, prolong absorption and improve drug therapy performance.

This study aims to formulate a sprue gel from betel leaf extract by varying carbopol 934 and xanthan gum as a gelling agent.

2 Research Methods

This type of research is experimental research conducted in the laboratory, by making 3 types of thrush gel formula containing 10% betel leaf extract and variations of carbopol 934 and xanthan gum as gelling agents, as well as physical stability tests and skin irritation tests.

The object of research is betel leaf extract, obtained by extracting green betel leaf simplicia. The betel leaves taken are perfectly green leaves, indicating the highest levels of active compounds so that good quality is obtained. The leaves that have been picked are separated from the impurities attached to the leaves and discarded the parts that are not needed. Then the simplicia was washed with running water for as short a time as possible to remove dirt and microbes, but did not remove these efficacy substances. The betel leaf is chopped with a chopper without causing damage or loss of the required chemical content. Then the betel leaves are dried with aerated or not exposed to direct sunlight at room temperature. As it continued, it was extracted by maceration with 96% ethanol.

Furthermore, the betel leaf extract was formulated into a gel preparation. The formula used in this study was based on the thrush gel formula of [9] from saga leaf extract (Abrus precatorius L.). Three formulas were made with 10% betel leaf extract concentration as the active ingredient, in accordance with the results of research from [10], and variations of carbopol 934 and xanthan gum as gelling agents (Table 1).

Table 1. Sprue gel formula containing betel leaf extract (Piperis betle L.)

Ingredients	Control Formula (%)	Formula I (%)	Formula II (%)	Formula III (%)	Function
Betel leaf extract	-	10	10	10	Active substance
Liquid sorbitol	10	10	10	10	Humectant
Gliserin	10	10	10	10	Humectant
Carbopol 934	0.5	1	1.25	0.75	Gelling agent
Xanthan gum	0.5	1	0.75	1.25	Gelling agent
TEA	0.75	0.75	0.75	0.75	Alkali marker
Nipagin	0.1	0.1	0.1	0.1	Preservative
Potassium sorbate	0.1	0.1	0.1	0.1	Preservative
Aquadest ad	100 ml	100 ml	100 ml	100 ml	Solvent

Preparation of thrush gel formula from betel leaf extract by dissolving nipagin with hot aquadest 20 times the weight of nipagin, stir until homogeneous. Add potassium sorbate, stir until dissolved and homogeneous (preservative solution). Expand xanthan gum in aquadest as much as 20 times its weight, stir until it expands and is homogeneous, do it on a water bath at a temperature of 50 °C. Add preservative solution, stir until homogeneous (mass I). Develop carbopol 934 in warm aquadest 20 times the weight of carbopol, stir until homogeneous and expands. Add triethanolamine (TEA) and glycerin, stir until homogeneous (mass II). Enter mass II into mass I, stir until homogeneous. Add liquid sorbitol, stir until homogeneous (mass III). Dissolve the betel leaf extract with sufficient aquadest, stir until dissolved and homogeneous. Enter into mass III little by little, stir until homogeneous. Add the remaining aquadest, stir until homogeneous.

Evaluation of sprue gel preparations betel leaf extract includes organoleptic observations (by observing the color and odor of the test preparations), check pH, the viscosity test, homogeneity, spreadability, syneresis/swelling, and skin irritation test. Evaluation of physical stability was carried out on each formula at week 0, 1, 2, 3 and 4 at room temperature.

3 Results and Discussion

Betel leaf extract (Piperis betle L.) has been formulated into a gel preparation for the treatment of canker sores. Betel leaf that has been chopped and dried is obtained as much as 952 g, then extracted by maceration using 96% ethanol as a solvent.

First, the simplicia is finely chopped, to break down the cell walls and increase the surface area of the simplicia in contact with the solvent, so that the solvent enters the cells more easily, and then the active substance moves from the cell into the solvent. The solvent used is 96% ethanol because the active substance content of the betel leaf is polar, namely saponins, flavonoids, and polyphenols. Ethanol is a polar solvent so that it allows the active substance to be dissolved.

The thick extract of betel leaf obtained was 243 g, with an extract yield of 25.52%. The yield obtained is greater than the research by [10], which is 19.2%.

Evaluation of the betel leaf extract gel included pH, viscosity, homogeneity, dispersibility, syneresis/swelling, color, odor, and skin irritation test. Evaluation of physical stability was carried out every week until the 4th week of storage. The results of the evaluation of betel leaf extract gel can be seen in Table 2.

Measurement of pH using a pH meter. Gel pH testing showed that all gel formulas had a pH that met the requirements for the pH of the oral mucosa from 5.5 to 7.9 [11]. In the control formula there was an increase in pH each week of storage, on the contrary in formulas I, II, and III there was a decrease in pH each week of storage. The pH range of the control formula is 7.06–7.22 (2.27%), formula I has a pH range of 6.01–6.25 (3.84%), formula II has a pH range of 5.57–6.30 (11.59%), formula III has a pH range of 6.21–6.71 (7.45%). From the percentage change in pH, it can be seen that formula I tends to be more stable than formula II and formula III.

The pH range obtained is not too much different from the research of [9] regarding gel for thrush from saga leaf extract (Abrus precatorius Linn.), where the pH range is 6.47–6.72, while the pH range of betel leaf extract gel is 5.57–6.71. This difference is due to differences in the concentration of the extract used, where the concentration of saga leaf extract used is 1%–5% while the concentration of betel leaf extract used is 10%.

The pH of sprue gel preparations is closely related to the stability of the gelling material, carbopol 934 will form a gel mass that is stable at pH 6–11 and xanthan gum is stable at pH 4–10 [8].

Viscosity testing on gel preparations aims to determine whether or not the preparation is easy to apply which is indicated by its ability to flow. Viscosity can affect the spreadability of a preparation. The viscosity of gel preparations generally ranges from 6,000–50,000 cp [12]. Viscosity measurement using a brookfield viscometer.

During 28 days of storage, the viscosity of the gel preparations in the control formula decreased, while the viscosity of formulas I, II, and III increased. The viscosity of the control formula has a range of 9,137–7,942 cp (13.08%). The viscosity of formula I has a range of 15,586–17,205 cp (10.39%). The viscosity of formula II has a range of 14,782–17,832 cp (20,63%). The viscosity of formula III has a range of 14,539–15,910 cp (9,42%). The viscosity of formula III is more stable than the viscosity of other formulas. All formulas have a viscosity that meets the requirements (6,000–50,000 cp).

From the observations, the highest viscosity of the preparation until the 28th day was in formula II with a concentration of carbopol 934 was 1.25%, followed by formula I with a concentration of carbopol 934 was 1%, and the lowest viscosity was in formula III with the concentration of carbopol 934 is 0.75%. This indicates that the higher the concentration of carbopol 934 used, the higher the viscosity of the gel preparation [8], because carbopol 934 forms a gel base by absorbing the solvent so that the liquid is retained.

It can also be seen that formulas I, II, and III containing betel leaf extract have higher viscosity than control formulas that do not contain extracts, it is suspected that the addition of extracts to the gel base will increase the viscosity [13].

Table 2. Recapitulation of the results of evaluation of betel leaf extract gel

gel	Physical stability test							Skin irritation test	total	
	pH	Viscocity (cp)	Homogeneity	Dispersibility (cm)	Syneresis/swelling	color	odor		ms	Tms
Control Formula	7.06–7.22 (MS)	9,137–7,942 (MS)	MS	6.3–6.7 (MS)	MS	MS	MS	MS	8	0
Formula I	6.01–6.25 (MS)	15,586–17,205 (MS)	MS	5.6–5.3 (MS)	MS	MS	MS	MS	8	0
Formula II	5.57–6.30 (MS)	14,782–17,832 (MS)	MS	5.7–5.1 (MS)	MS	MS	MS	MS	8	0
Formula III	6.21–6.71 (MS)	14,539–15,910 (MS)	MS	5.7–5.3 (MS)	MS	MS	MS	MS	8	0

MS = according to requirements
TMS = not eligible

The gel homogeneity test was carried out by applying a thin layer of gel to the object glass, then covered with a glass deck. Then the distribution of the particles was seen under a microscope at a magnification of 100X. It is said to be homogeneous if the particles are seen to be evenly distributed.

The results of the homogeneity test showed that all gel formulas had particles that were well distributed in the gel base, as seen from the absence of lumpy or uneven particles in the control formula, formula I, formula II, and formula III for 28 days of storage.

The dispersion test of the preparation aims to determine how well the gel preparation spreads on the surface of the skin, because it can affect drug absorption and the speed of release of the active substance at the site of use. Good dispersing ability will provide a good application on the surface of the skin, besides that the distribution of the active ingredients on the skin is more even so that the effects of the active ingredients become more optimal.

Testing the spreadability of the gel was carried out by placing 1 g of the gel preparation in the middle of an inverted petri dish, then covered with plastic. Then put a weight of 125 g on it and leave it for 1 min. Then the diameter of the spread of the gel was measured using a ruler and the diameter of the spread was recorded. The test was carried out 3 times. The dispersion diameter that meets the requirements for gel preparations is 5–7 cm [14].

The results showed that the control formula's gel spreadability was 6.3–6.7 cm, an increase of 6.35% until the 4th week of storage. The spreadability of the gel formula I was 5.6–5.3 cm, decreased by 5.36% until the 4th week of storage. The spreadability of the gel formula II was 5.7–5.1 cm, decreased by 10.53% until the 4th week of storage. The spreadability of the gel formula III was 5.7–5.3 cm, decreased by 7.02% until the 4th week of storage.

The results of the spreadability test of all formulas for each week showed that formula I was the most stable among other formulas, but all formulas met the requirements for the spread of 5–7 cm [14].

The decrease in the spreadability of the betel leaf extract gel was related to the increase in gel viscosity and the use of gelling agent. The higher the concentration of gelling agent used, the viscosity will increase and the spreadability will decrease [14]. Formula II with the highest number of carbopol 934 showed the lowest dispersion and the highest viscosity in the fourth week.

The syneresis phenomenon is caused by the water contained in the gel preparation not being completely dispersed in the polymer so that it is susceptible to separation during storage. Meanwhile, swelling is caused by moist storage so that the gel more easily absorbs water from the air which causes an increase in the volume of the gel [15]. The syneresis and swelling test showed that there was no syneresis and swelling in all formulas for 28 days of storage.

Tests on the stability of the color and odor of the gel formula were carried out by observing by 30 respondents on the gel preparations that were stored for 0 weeks to 4 weeks. The results of the respondent's observations are written on the distributed questionnaire.

The control formula has a clear color and does not have a distinctive odor, because betel leaf extract is not added. Meanwhile, formula I, formula II, and formula III have a greenish color and a distinctive odor from betel leaf extract.

The results of the color stability test of the betel leaf extract gel showed that there were as many as 96.67% of respondents who stated that there was no color change in formula II, while in the control formula, formula I, and formula III there were 100% of respondents who stated that there was no color change during 28 days of storage. Tests on the odor stability of the gel showed that all respondents stated that there was no change in odor in all formulas during 28 days of storage.

The skin irritation test was carried out on 30 respondents by applying a gel on the back of the respondent's hand and then waiting for a while to see if there was an allergic reaction such as itching, burning, or redness. The test results on the control formula, formula I, and formula III showed that all respondents did not experience irritation. While in formula II there were as many as 96.67% of respondents who stated that there was no irritation after a few minutes the betel leaf extract gel was applied.

After testing the physical stability and irritation test on the betel leaf extract gel (Piperis betle L.), it can be seen that formula I, formula II, and formula III meet the requirements for pH, viscosity, homogeneity, dispersibility, syneresis and swelling, color stability, odor stability, and skin irritation test. Formula I is the most stable formula compared to formula II and formula III.

4 Conclusion

Betel leaf extract (Piperis betle L.) can be formulated into a gel preparation that is stable and meets the requirements. The most stable combination of carbopol 934 and xanthan gum is in formula I with a concentration ratio of carbopol 940 and xanthan gum 1%: 1%.

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